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Some Recent Research on the Heart and Circulation

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A BRANCH of physiology which has recently had much attention is fœtal physiology. In choosing to start with the fœtus, then, it is because it is convenient to do so, though I cannot deny that I am proud to say that the work formed the subject of the John Mallet Purser Lecture, Trinity College, Dublin, given last year by my father.[1]

The fœtuses used for the investigations were lambs or kids of known intrauterine age. They were removed from the mother by Cæsarean section. A very important point was that after delivery they were placed in a bath of warm saline and the cord was not tied. For this reason the fœtus continued to get its oxygen from the placental circulation and did not breathe. At any desired moment it could be "born" by tying the cord; breathing ensued after a pause of rather less than a minute. At the risk of too much digression, I might mention that the essential stimulus for fœtal respiration was found to be oxygen lack; carbon dioxide accumulation, per se, was ineffective.

FŒTAL BLOOD-PRESSURE.

The following data may be taken as typical of the carotid arterial pressure of fœtal sheep of different intrauterine ages, full term in the sheep being about 140 days :—

Fœtal age in days - - -	49	101	120	123	137	138	140
Carotid arterial pressure in mm. Hg.	20	34	46	50	72	68	76

During the last six weeks of pregnancy the fœtal arterial pressure was doubled. The arterial pressure at full term, about 75 mm. Hg., is, however, very different from that of the new-born lamb. After "birth," that is, ligature of the cord, the pressure rises another 20 mm. Hg. at about the same time as breathing starts, so the pressure in the new-born lamb is about 100 mm. Hg. It is interesting to observe that the stage of development of the blood-pressure at birth is more advanced in

the lamb than in the baby. Bowman's[2] readings of a baby's systolic pressure on the first four days of its life are 55, 60, 60, 60 mm. Hg. respectively.

The Path of the Fœtal Blood-Stream.

The anatomists have given us the classical picture of the path taken by the fœtal blood-stream. They have deduced the course of the stream from the colour of the blood in the main blood-vessels. Red arterial blood from the placenta enters the right auricle, passes through the foramen ovale, and is propelled by the left ventricle through the carotids round the upper part of the body. Blue venous blood returning from the upper part of the body enters the right ventricle, and is propelled through the pulmonary artery and ductus arteriosus down the thoracic aorta into the trunk and placenta. These conclusions were tested by my father on the fœtal sheep.

At the chief points at which two tributary streams converged to form a main stream, and at which a main stream divided to form two tributary streams, the amount of oxygen in the blood of both the main stream and its tributaries was measured. By comparing the composition of the three streams, the relative rates of the streams in the tributaries could be determined. The results, which I quote verbatim from the Purser Lecture, were as follows :—

"1. The blood which passes through the heart may be regarded as forming two streams approximately equal in volume.

"2. One of these goes to the 'head,' and is not much inferior in its oxygen content to the redder blood which reaches the heart; namely, that coming along the inferior vena cava.

"3. The second, which is not much redder than the venous blood from the 'head,' goes to the 'body,' which means the lower part of the trunk and placenta.

"4. Of the blood going to the 'body,' about two-thirds goes to the placenta."

Actual measurement, therefore, confirms the deductions drawn from inspection.

There is a further interesting implication. It will be seen from the conclusions above that the blood-stream is divided among the chief territories of the fœtal circulation in the following proportions: "head," three-sixths; placenta, two-sixths; "body," one-sixth. In other words, the head or upper part of the body receives three times as much blood as the "body." A more exact idea of the territory supplied by the vessels of the "head" was obtained by ligaturing the aorta distal to the ductus arteriosus and injecting a dye into the left ventricle. "As well as the actual head and arms, the whole of the chest-wall was injected, and, what was very interesting, the coverings of the spinal cord, down almost to the lumbar swelling. Thus all the organs which at this stage of fœtal life are functionally important, except the liver and lowest section of the cord, can receive reddish blood from the upper circulation."

The Closing of the Ductus Arteriosus.

The effectiveness of the normal type of respiration which establishes itself at birth depends upon the rapidity with which the circulation changes from the fœtal

to the normal. This change involves the closing of the ductus arteriosus. The patency of the ductus arteriosus was investigated before and after "birth." Whereas it was wide open before tying the cord, it was found to be tightly closed a short time after. The mechanism for closing the ductus rapidly is not yet plain. It is true, however, that the histology of the ductus is quite different from that of the neighbouring blood-vessels—its walls are much more muscular.

The patency of the ductus arteriosus before birth implies that the right and left intraventricular pressure must be much the same, approximately 75 mm. Hg. This means that the fœtal right ventricular pressure is about 50 mm. higher than that of the adult.

The Cardiac Output in Man.

The "cardiac output" may be defined as the volume of blood ejected from the left ventricle in one minute. It is an index of the function of the heart, which is to supply blood to the periphery. The "acetylene" method, introduced by Grollman,[3] has recently been used for measuring the human cardiac output in a very wide range of physiological, pharmacological, and pathological conditions.

The principle of the method is briefly as follows. The volume of oxygen absorbed in the lungs in one minute (*a*), divided by the volume of oxygen which leaves one litre of blood in the peripheral circulation (*b*), gives the number of litres of blood transversing the lungs in a minute, that is, the cardiac output. The oxygen intake (*a*) is found by one of the methods ordinarily used for B.M.R. determinations. The "arterio-venous oxygen difference" (*b*) can be calculated from analyses of a mixture of air and acetylene which the subject rebreathes from a rubber bag. In practice the method is valuable, because the subject needs no training, and the measurements and calculation take only a few minutes. The author states that the method has an error of less than ten per cent.

Further remarks on the cardiac output under a variety of conditions may well be prefaced by saying that for a given individual, under basal conditions, the values are surprisingly constant. Over a period of nearly two years, determinations were done on a healthy young man about ten minutes after waking up and before getting out of bed. The average cardiac output was 3.9 $\pm$ 0.02 litres per minute (maximum variations). In this man the extreme variations in the cardiac output amounted to about six per cent.; the variation in his basal pulse, taken at the same time, was thirteen per cent.

Mild Exercise and Massage.

The effect of exercise on the cardiac output has been the subject of numerous investigations. The findings, in general, have pointed to the fact that the cardiac output is proportional to the oxygen consumption. Grollman's interesting experiments on the cardiac output in mild exercise throw a new light on the subject. The nature of the exercises and the oxygen consumption and cardiac output findings are shown in the following table :—

Experiment No.	*Exercise*	*Oxygen consumption in c.c. per minute*	*Cardiac output in litres per minute*
1	Resting - - - - -	246	4.1
2	Flexing and extending right forearm once per second - - - -	286	4.8
3	Alternately flexing and extending both forearms, each every other second -	315	4.3
4	Flexing right thigh once per second -	430	7.7
5	Alternately flexing both thighs each every other second - - - -	428	5.0

In experiments 2 and 3 the same number of "forearm bends" were done in a minute. The cardiac output, however, was greatest when all the bends were done with the same forearm. The oxygen consumption was greater when both forearms were used. The "leg-bend" exercises show the same thing, namely, that a given number of bends in a minute increase the output more if done with one leg than with two. The oxygen consumption was practically the same whichever way the leg exercises were done. One sees that in these experiments the cardiac output is more closely related to the rapidity with which groups of muscles are moved than to the oxygen consumption. A muscular contraction squeezes the blood towards the heart; on relaxation reflux is prevented by the valves in the veins. Rapid contraction increases the efficiency of this muscle "pump."

These results throw some light on the vascular effects of massage and passive movements. Liljestrand and Stenstrom found the oxygen consumption of one subject increased from 261 to 322 c.c. during massage of the shoulder muscles, to 285 c.c. during abdominal massage, and to 379 c.c. during passive movements. Does the cardiac output follow the increase in oxygen consumption? Pap found that there was no increase in the circulation in a massaged area, unless it was congested. In the light of Grollman's experiments on mild exercise, this could be explained by the reasonable supposition that massage does not return the blood to the heart nearly as effectively as natural muscular contraction; increased oxygen consumption, per se, is not a reliable index of increased flow. Further work on the cardiac output before and after massage will be valuable.

Baths and Heart-"Strain."

It is generally recognized that very hot baths are bad for invalids. It is interesting to see that the temperature of the bath water has a considerable effect on the cardiac output. Cold baths depress the output, but in some people hot baths may increase it by over three hundred per cent., an increase which would put more strain on the heart than other demands incurred in everyday invalid life such as meals, excitement, and mild exercise. Bath temperatures and cardiac outputs are shown in the following table:—

Experiment No.	*Temperature of bath, in degrees Centigrade*	*Cardiac output in litres per minute*
1	32.5	3.20 (before bath)
		6.93 (during bath)
2	38.0	3.76 (before bath)
		12.50 (during bath)
3	38.5	3.60 (before bath)
		5.69 (during bath)
4	22.5	3.06 (before bath)
		2.81 (during bath)

Insulin and Cardiac Output.

Several clinicians have called attention to the occurrence of circulatory shock and even death from heart failure during insulin hypoglycæmia. Ernstene and Altschule injected forty to eighty units of insulin into sixteen normal subjects, aged between 16 and 45; they noted the effect of the injection on the cardiac output. In all cases the output was increased. The increase varied from three to eighty-six per cent., with an average of twenty-nine per cent. Grollman draws attention to the danger of large doses of insulin, likely to produce hypoglyæmia, in cardiac cases.

Cardiac Output and Digitalis.

In agreement with Lundsgaard, Grollman finds that the cardiac output in valvular disease of the heart is diminished when signs of failure are present. The diminution may be up to fifty per cent., depending on the degree of failure. The "acetylene" method has been used by Stewart and his co-workers to assess the value of digitalis therapy in heart cases. As heart failure leads to a diminution in cardiac output, which in its turn leads to the manifestation of the signs of heart failure in the other organs, cardiac output measurements are the most important pharmacological index of the value of therapeutic agents in heart-disease.

The effect of digitalis (0.8-1.0 gram of digitan) was first tried on normal people. After four hours there was a *decrease* in the cardiac output, which was greatest after twenty-four hours and had disappeared after forty-eight hours. The pulse and area of the heart by X-ray were also decreased, and one subject experienced dyspnœa and cardiac pain on slight exertion. In normal subjects, therefore, digitalis puts the circulation at a disadvantage.

Quite the opposite findings occurred in cases of heart failure. "Thus in one patient with heart failure of the congestive type, and a clinical diagnosis of generalized arterio-sclerosis, hypertension, rheumatic heart-disease (mitral insufficiency), and cardiac hypertrophy, the cardiac output in the basal resting condition was 2.88 litres per minute, which corresponds to an abnormally low cardiac index* as occurs in heart failure. The cardiac area was 198.3 sq. cm. Administration of digitalis (1.0 gram of digitan) resulted in an increase in the cardiac output to 3.54 litres per minute, a decrease in cardiac area to 180.2 sq. cm., a slowing of the pulse, and

* Cardiac output per square metre of surface area.

alterations in the form of the T-wave of the electro-cardiogram. As the effects of digitalis wore off, the signs of heart failure reappeared, accompanied by a decrease in the cardiac output in the course of two weeks to 2.62 litres, and an increase in the cardiac area to 193.6 sq. cm. When digitalis was administered a second time, results similar to those first observed were obtained." It appears from these results that digitalis is only of value in heart failure; in the absence of failure it may even be contra-indicated. I believe it is correct to say that is in accordance with clinical experience.

The Mechanism of Digitalis Bradycardia.

This has recently been investigated by Heymans,[4] the leading authority on the physiology of the carotid sinus.

Dogs whose carotid sinus nerves are cut make a rapid recovery from the operation. They differ from normal animals, as they have chronic tachycardia and hypertension. The heart-rate in the normal dog is about ninety a minute; after denervation of the sinuses it is about 250. The normal and the sinus-denervated animals behave differently after the administration of the digitalis compounds. After an intravenous injection of 0.03 milligrams of ouabaine per kilo body-weight, the heart-rate of a typical normal dog fell from 100 to 64, a reduction of about forty per cent. In the denervated animals a typical effect of the same dose of ouabaine decreased the heart-rate from 270 to 260, a slowing only amounting to four per cent. Since denervation of the carotid sinuses almost abolished the digitalis bradycardia, Heymans seems fully justified in concluding that the bradycardia is due to the action of digitalis on the sinuses. According to his teaching, the heart-rate in normal animals is permanently kept in check by a reflex from the sinus; this reflex is due to the pressure of the blood upon sense-organs in the sinus walls. Heymans' view is that digitalis increases the sensitivity of the sinus sense-organs, and for this reason the normal blood-pressure elicits an exaggerated reflex inhibition of the heart.

The Pulse in Exercise.

I have already referred to the relationship between cardiac output and oxygen consumption in exercise. This section describes some recent work on physiology of the heart-rate during activity.

Muscular work and increase in the pulse are always associated with each other. This partnership invites the conclusion that increase in the pulse is necessary for the proper function of the heart in exercise. Although it is true that cardiac output may be increased from three to as much as thirty litres per minute—is the increase in the pulse essential? A second question of interest is the cause of the increase in the pulse; so many factors are known to affect the heart-rate that the relevant ones and their comparative importance are not obvious. Experiments on these problems were done in Heymans' laboratory by Adli Samaan;[5] I was fortunate to be his colleague in another investigation at University College.

Samaan's scheme was to count the increase in the pulse in normal dogs in exercise, and then to repeat the observations after cutting one or more of the nerves which might be causing tachycardia.

The type of exercise was carefully controlled. Each dog had its own "standard exercise," and also did a "maximum endurance test." Both exercises were done in a treadmill driven at a constant speed. The "standard exercise" lasted double the time which elapsed before panting began. In the "maximum endurance test" the dog ran on the treadmill until it was tired; the duration of running was expressed in multiples of its "standard exercise" time. In every case the heart-rate was recorded at rest and just before the end of the exercise. An electro-cardiographic method was used. Typical results are shown in the following table :—

Series	*Operation*	*Resting Pulse*	*Pulse at end of standard exercise*	*Increase in pulse during exercise*	*Maximum endurance in multiples of standard exercise time*
1	Normal dogs - - -	90	230	140	3
2	Vagotomy or atropine - -	200	280	80	1
3	Cardiac sympathectomy -	70	140	70	8
4	Suprerenal glands denervated -	90	170	80	3
5	Vagotomy or atropine, cardiac sympathectomy, suprarenal glands denervated - -	120	130	10	2
6	Vagotomy or atropine, suprarenal glands denervated -	185	210	25	1

In the first place, the experiments show the very strong tonic influence of both the vagus and sympathetic on the resting heart. The natural resting rhythm of the S.A. node in the denervated heart (series 5) is about 120 per minute. With vagi cut but sympathetic intact (series 2) it is 200. It is the imposition of very strong vagal tone which brings the pulse down to 90 in normal resting dogs (series 1).

The table also shows that the following three factors contribute to the acceleration of the pulse in exercise :—

1. The vagus nerve. After vagotomy the increase in the pulse in exercise was reduced from 140 to 80 (series 2).
2. The sympathetic supply to the heart. After sympathectomy the increase in the pulse was reduced to 70 (series 3).
3. The secretion of adrenaline. After denervation of the suprarenals the increase in the pulse in exercise was reduced to 80 (series 4).

This is confirmed by the fact that after complete denervation of the heart and suprarenals, exercise produces a negligible increase in the pulse, only ten beats (series 5). This slight increase may be explained by the rise in temperature of the blood acting directly on the S.A. node.

The most important factor in the increase in the pulse in exercise is the removal of the vagal tone, which allows the sympathetic tone full play. The increase in sympathetic tone in exercise is surprisingly slight, as can be seen in series 6, after vagotomy and denervation of the suprarenals. In these animals the acceleration of the pulse in exercise could only be due to excitation of the heart by increased sympathetic tone, and the acceleration only amounted to twenty-five beats per

minute. The secretion of adrenaline also plays a definite but subsidiary rôle in quickening the heart.

The maximum endurance test has a point of remarkable interest. It will be seen that the normal dogs could run for three times the duration of their standard exercise before the onset of fatigue. The dogs with the sympathetic supply to their hearts cut (series 3) could last out *eight* times the duration of their standard exercise. This means that a dog with a cardiac sympathectomy has nearly three times the endurance of a normal dog. Does this mean that a gold mine is waiting for the owner of a stud of sympathectomized racehorses? On the other hand, vagotomy reduces the maximum endurance: the dogs are "done" at the end of the standard exercise. It is very difficult to see why sympathectomy and vagotomy should have these effects. It does not seem to be due to their influence on the heart-rate. A. V. Hill has shown that the limiting factor in the duration of exercise in man is the cardiac output, which, in its turn, is limited by the oxygen supply of the heart. As the sympathetic nerve conveys dilator impulses to the coronary vessels, one might suppose that section would prevent full coronary dilatation in exercise, and so limit the cardiac output and maximum endurance. In point of fact, sympathectomy has a beneficial effect. Further inquiry into this paradox will be valuable.

Lastly, the normal tachycardia of 230 in exercise does not seem to be necessary for the proper execution of the exercise. In the sympathectomized dogs the pulse was only 140, yet they had a greater capacity for exercise than normal dogs.

Metabolism of the Heart.

This problem of great physiological interest is beset with practical difficulties. Recently much valuable progress has been made by A. J. Clark,[6] at present external examiner in pharmacology at Queen's University. Much is already known about the metabolism of skeletal muscle; Clark's work has illuminated certain similarities and differences in that of cardiac muscle. Owing to the difficulty of experimenting with mammalian hearts, Clark's work was done with frog and tortoise hearts.

The salient points of the metabolism of a skeletal muscle during contraction are shown in the following equations:—

$$\text{Phosphagen} = \text{phosphoric acid} + \text{creatine}$$
(energy for contractile process).

$$\text{Glycogen} = \text{lactic acid}$$
(energy for phosphagen resynthesis).

$$O_2 + \text{lactic acid} = CO_2 + H_2O$$
(energy for resynthesis of four-fifths lactic acid).

The energy for a contraction is set free by the breakdown of some of a small store of phosphagen. This is followed almost at once by the breakdown of a little of the large store of glycogen to lactic acid. The formation of lactic acid releases energy which is used for the immediate resynthesis of the phosphagen. When oxygen is available, as it normally is, one-fifth of the lactic acid is oxidized to CO_2 and water; the large amount of energy liberated by this oxidization is used to resynthesize the remaining four-fifths of lactic acid to glycogen.

Under "anærobic" conditions, fatigue sets in sooner, but a great number of contractions can still be carried out; the phosphagen cycle and the breakdown of glycogen to lactic acid go on as usual, but the lactic acid cannot be resynthesized.

When muscle is poisoned with iodoacetic acid, lactic acid formation is stopped; only a few contractions are possible, as the small store of phosphagen is soon broken down and cannot be restored in the absence of lactic acid formation.

One of Clark's important discoveries is that the energy for the contractile process of heart-muscle is, like that of skeletal muscle, derived from the breakdown of phosphagen. A minor point of difference between the two types of muscle is that when skeletal muscle is active a little of the phosphoric acid and creatine escape into the blood; under similar conditions no phosphoric acid escapes from the heart. As regards phosphagen, then, the main thing is that in both types of muscle it supplies the energy for the contraction itself.

Under anærobic conditions the frog's heart may go on beating for many hours. There is a loss of glycogen from the muscle, and lactic acid is formed. Glucose added to the perfusion fluid is taken up by the heart and used for lactic acid formation. If iodoacetic acid is added to the perfusion fluid (anærobic) the heart stops in a few beats, because lactic acid cannot be formed, and so phosphagen cannot be resynthesized. One may go as far as to say that under *anærobic* conditions the metabolism of heart and skeletal muscle is much the same. Both derive the energy for phosphagen resynthesis from one and the same reaction—the breakdown of glycogen to lactic acid.

The "ærobic," and hence the normal, metabolism of heart and skeletal muscle differ. Iodoacetic acid stops skeletal, but not cardiac muscular contraction. This substance, as previously mentioned, prevents the formation of lactic acid from glycogen. The implication is that under *ærobic* conditions the heart is not dependent on the breakdown of its glycogen for the provision of energy for phosphagen resynthesis: the energy can be drawn from another source, not available in skeletal muscle. It is naturally very important to know if glycogen metabolism plays any significant part in the normal heart. According to Clark, only about forty per cent. of the oxygen used by the ærobic heart may be regarded as taking part in the oxidization of carbohydrate. Thirty-six per cent. of the oxygen consumption provides energy by combusting protein; the remainder combusts some unknown material, which, however, is not fat. Further important developments may be expected in this field.

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